Written Comments to the EPA Science Advisory Board

on May 13, 2010 Draft Report

Submitted by the Inorganic Arsenic Cancer Review Work Group

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The Office of Advocacy submits these comments regarding the May draft report submitted by the Inorganic Arsenic (iAs) Cancer Review Work Group. The Office of Advocacy was established pursuant to Pub. L. 94-305 to represent the views of small entities before Federal agencies and Congress. Advocacy is an independent office within SBA, so the views expressed by Advocacy do not necessarily reflect the views of the SBA or the Administration.

This Work Group was convened in order to present additional recommendations on the implementation of certain key 2007 Science Advisory Board (SAB) recommendations regarding the draft 2010 "Toxicological Review of Inorganic Arsenic: In Support of the Summary Information on the Integrated Risk Information System (IRIS)." This draft assessment includes an evaluation and characterization of the potential cancer hazard of inorganic arsenic and a quantitative dose-response cancer assessment for iAs.

Unfortunately, EPA did not seek a comprehensive review of the draft arsenic assessment, rejected requests to expand the charge, and, in the end, did not obtain a comprehensive review from this Work Group. The Agency procedures separately and collectively had the effect of minimizing the opportunity for a true and robust independent review of even the limited issues specified in EPA's "focused" charge to the Work Group.

Advocacy believes that the SAB, as the independent reviewer of EPA science assessments, must reject this extremely poor effort. Based on the draft review comments and the discussion at the Work Group meeting on April 6 and 7, we find no evidence that the Work Group made a serious attempt to evaluate or consider the significant objections to the EPA Assessment raised by the public presenters at the April 6th meeting. Not one commenter supported the EPA Assessment. These presenters were among the most knowledgeable arsenic scientists in the country. We find this very surprising and disconcerting. By apparently not considering the very significant adverse comments by the presenters, the Work Group failed to discharge its obligations to perform an independent review.

These actions by EPA and the Work Group are not consistent with achievement of scientific integrity and transparency, two major EPA goals. In order to obtain a truly independent and robust review of the new science assessment, the Agency should have implemented procedures designed to enhance and not minimize review by the affected public and the Work Group. The SAB should have the opportunity to complete an updated science review, including new significant work that should be completed within about one year, with a full and comprehensive charge.

I. Background

Advocacy commented on the arsenic cancer assessment as early as 2001, when EPA initially considered lowering the drinking water standard from 50 ppb to 10 ppb.[1] At that time, we expressed concern that the evidence supporting a significant risk below 50 ppb was in substantial question. In the last ten years, much evidence has come forth supporting a drinking water threshold effect at greater than 50 ppb. This was demonstrated by the scientists who testified at the April 6th work group meeting regarding the international evidence from the U.S., Southwestern Taiwan, Chile and Argentina, the meta analysis by Mink et al., and the mode of action literature supporting a drinking water threshold. If EPA finalizes this new cancer potency factor, it will increase the cancer potency factor by a factor of 7 compared to the drinking water standard slope, and a factor of 17 over the current IRIS potency figure.

A. Impact of Revision of Arsenic Cancer Slope Factor

Why does this matter to small businesses? A change of the cancer potency (or cancer slope factor) would substantially raise the number of small water systems required to spend substantial resources to lower arsenic concentrations without any potential benefits. It also would substantially affect the number and cost of Superfund cleanups involving arsenic, a naturally occurring metal in the soil. Furthermore, it could raise unnecessary public concerns about whether the food supply can safely contain small traces of arsenic. Therefore, small businesses have a large stake in EPA using the best science.

B. History of Arsenic Review

EPA completed a review of inorganic arsenic in 2005, and has been working since 2007 to implement the very significant recommendations of the June 2007 SAB report. In February 2010, after an almost three year delay in updating the 2005 report, EPA issued a new draft report for review. However, instead of allowing a full review of this report, and an adequate time frame, after a three year delay, EPA suddenly announced a "focused review" of several narrow issues, and permitted the public barely more than one month to review the 575 page IRIS assessment. It denied requests to allow more time or to allow a more comprehensive review. After years of delay, we are baffled regarding EPA's justification for this truncated public review.

As Mr. B. Smarte pointed out in his comments on the 2010 draft, this Work Group review could give the public the misimpression that the SAB is making a "complete endorsement of the EPA's revisions and scientific determinations." Indeed, even the normally careful BNA, on May 25, used the headline: "Panel Endorses EPA Draft Assessment of Cancer Risk from Arsenic Exposure." However, this Work Group didn't comprehensively review the modeling or the scientific determinations nor, in the view of

[1]Letter from Susan Walthall, Acting SBA Chief Counsel for Advocacy, to EPA Administrator Christine Whitman, dated March 27, 2001.

many observers, did it even do justice to the limited charge. Advocacy agrees with others that it appears that the draft Work Group is more of an attempt to reinforce the credibility of the EPA document, rather than perform an independent scientific review.

The SAB should reassert its historical role as an independent arbiter of scientific analysis at EPA. The 2007 SAB report was an excellent example of a true and robust independent review. The contrast between that report and the Work Group review could hardly be stronger. If the SAB simply affirms the work group review, the SAB would not be acting as independent reviewers, and would cede its role to other peer review bodies, such as the National Academy of Sciences.

II. The Work Group Review Suffers from Many Procedural Deficiencies

The list of procedural infirmities for this review is both long and disturbing. Advocacy concludes that this review should be terminated, because this review does not significantly advance the state of iAs science. EPA may well be better served if it waits for the completion of new significant research to update the IRIS summary. We list below most of the procedural deficiencies known to us.

1. Despite the fact that EPA was working for three years on the latest draft assessment, EPA allowed the public, the SAB and the Work Group only a few months to complete its review and comment.

2. Instead of allowing review of all the critical scientific assumptions, inputs and methodologies, EPA narrowly crafted the charge questions, thus avoiding review of some very key questions, including questions that have not been peer reviewed since 2001.

3. The panelists were chosen by the SAB, and unlike the National Academy of Science (NAS), there was no public opportunity to examine the candidates or suggest alternative panelists with relevant backgrounds.

4. EPA excluded all panelists from the 2007 SAB panel from the new review, despite the fact that these individuals had spent considerable time already learning about inorganic arsenic issues, and could have helped the new panel grasp these challenging issues.

5. In the first of two speaking opportunities, on April 6, witnesses were allowed only five minutes. There was no time to have any conversation between the panelists and the witnesses. At the second opportunity before the chartered SAB on June 16th, speakers are allowed only three minutes or less, and a dialogue in this forum is even less likely.

6. Due to a misunderstanding between Office of Research and Development (ORD) and the SAB about the ORD docket, the SAB failed to provide all the public comments to the Work Group until after the conclusion of the April 6/7 meeting.[2]

7. The minutes from the April 6/7 meeting will not be available in time for use by public commenters for the June 9 written comments.

8. Although this has been standard practice in peer review at the NAS and in some past SAB meetings, the Work Group should have reviewed and approved or revised the EPA charge to the Work Group. This did not occur. The 2005 Arsenic SAB panel did explicitly consider revising the charge, but decided not to do so.[3]

9. The Agency declined to expand the charge questions or provide more time for the public comment periods.

10. Five members of the 2005 SAB panel, which had produced a creditable and valuable report in 2007, were highly critical of certain aspects of the draft 2010 Review, and yet their concerns were apparently overlooked by the Work Group.

11. Most importantly, there was no apparent attempt by the Work Group to address the serious science objections raised by the scientific testimony at the meeting. No commenter supported the EPA assessment approach.

12. In conclusion, the Work Group appeared to take the role of editor in improving the technical detail of the document and make it more defensible, but missed the opportunity to seriously question many of the key scientific determinations (see below).[4] In addition, the Work Group did not have the opportunity to consider issues outside the limited EPA charge.

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[2] Given the apparent attempt to complete the report in large part during the April 6/7 meeting, the Work Group had limited opportunity to reflect on this misplaced set of comments, or the April 6 oral testimony.

[3] *Advisory on EPA's Assessments of Carcinogenic Effects of Organic and Inorganic Arsenic: A Report of the US EPA Science Advisory Board,* EPA SAB, Washington, D.C. (June 2007) at 1.

[4] Additional details about the procedural and scientific deficiencies of the Work Group process are found in the extensive comments filed by Dr. Michal Eldan for the Organic Arsenical Products Task Force on April 20, 2010 to the ORD/OEI docket. EPA-HQ-ORD-2010-0123-0019.1.

III. The Work Group Did Not Perform an Adequate Review of Key Science Issues, Including Issues Raised by the 2007 SAB Report

There are two questions raised by this review process: (1) Does the 2010 draft toxicological review truly conform with the 2007 SAB recommendations, or does more work remain even after this 2010 review process? and (2) Are there additional science questions that were not part of the 2007 SAB review that need to be part of an independent peer review?

The Federal Register notice announcing the June 16 SAB meeting states:

> ORD requested that the SAB evaluate and comment on EPA's interpretation and implementation of the key SAB (2007) recommendations. ORD requested a review focusing in three areas of the draft cancer assessment of inorganic arsenic: Evaluation of epidemiological literature; dose-response modeling approaches; and the sensitivity analysis of the exposure assumptions used in the risk assessment.[5]

The below discussion demonstrates both that the Work Group did not adequately address these three issues, including responding to key comments received in this area, and that other key science issues remain unaddressed. Both findings point to the termination of this work group review as not advancing the science, and not providing an independent and robust review of the EPA work product.

It doesn't require an in-depth analysis to determine that the draft 2010 EPA toxicological review omitted discussion or consideration of several key science concerns, and needs further work. This was and continues to be evident to the outside scientific community. The written comments by leading arsenic scientists presented to the Work Group support this conclusion. We submit below a few of the key issues that remain to be addressed in a properly executed peer review process to demonstrate that this review does not meet SAB standards for integrity and independence.

A. Evaluation of Mode of Action Literature

This is a key 2007 SAB recommendation that goes to the heart of the question of whether there is a nonlinear dose-response curve for iAs. Unfortunately, as was pointed out by the five members of the 2007 SAB panel that made the recommendation, the 2010 draft assessment does not implement the recommendation and the work group report simply "accepted EPA's choice" of using a linear approach.

[5] 94 Fed. Reg.27553, 27554 , May 17, 2010.

The 2010 SAB Work Group draft Report states:

> **Mode of Action and linear vs. non linear approaches**
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> The work group noted that *there is an ever increasing literature on arsenic, however there is not enough information in the literature to definitively describe a mode of action for the cancer endpoints of relevance for this evaluation [emphasis added]*. The work group notes that it is a reasonable hypothesis that bladder cancer is the result of repeated cell injury, cell death and compensatory proliferation, but there is not enough data at this point to confirm the hypothesis. Nor are there hypotheses to explain the role of arsenic in lung cancer. For these reasons, the work group concurred with EPA's rationale for choosing a linear approach for risk assessment.
>
> *Recommendation:*
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> Based on currently available information the work group accepted EPA's choice to retain a linear approach for their risk assessment.[6]

There is no evidence that the Work Group seriously reviewed the mode of action literature, and in its own words simply "accepted EPA's choice" to keep the linear approach. While the Work Group acknowledges that there is an "ever increasing literature" relevant to the mode of action, the required literature review was not documented in the 2010 draft toxicological review.

Five former members of that 2007 SAB Panel Review who filed comments with the 2010 SAB Work Group found:

> …no coherent critical integration and evaluation of these data is presented to address potential discrimination of key events in inorganic arsenic's carcinogenic mode of action. Meanwhile, other scientists have successfully evaluated, integrated and published critical reviews of this database.[7]

This is critical to the question of whether inorganic arsenic has a threshold (as the SAB found in 2007 for organic arsenic). EPA's 2005 Cancer Assessment Guidelines specifically states that EPA should seek independent scientific evaluation of this question. None was provided and none of the literature after 2007 was reviewed; further, some key studies prior to 2007 are missing from the 2010 Assessment.

Although many of the new mode of action studies were summarized in the 2010 Assessment, EPA does not provide elsewhere a critical evaluation of the weight of the evidence that supports a conclusion that "there is not enough data at this point to confirm

[6] May 13 Work Group Draft Report at 7.
[7] March 25, 2010 comment submitted by A. Barchowsky, et. al, EPA-HQ-ORD-2010-0123-0004.

the [threshold] hypothesis." Thus, if the Work Group had decided not to simply "[accept] EPA's choice," it could have discharged its obligation to render an independent review. A conclusory statement is not a weight of the evidence review using objective, clearly articulated criteria. The Work Group could simply have read and responded to the several public comments on this important point. But it did not do so.

B. Evaluation of Epidemiological Studies

The 2007 SAB report further recommended that EPA evaluate other recent published epidemiologic studies. Again, the five former 2007 SAB members wrote:

> Second, as cited in the February 2010 draft, while the SAB Arsenic Review Panel (2007) advised that the Taiwanese dataset (Wu 1989; Chen et al., 1988, 1992) "remains, *at this time*, (italics added) the most appropriate choice for estimating bladder cancer risk among humans, [due to exposure to inorganic arsenic] though the data have considerable limitations that should be described qualitatively or quantitatively to help inform risk managers about the strength of the conclusions." (SAB, 2007, p. 7). SAB (2007) also recommended that EPA evaluate other recent published epidemiology studies using a uniform set of criteria and document these findings in a weight-of-evidence assessment with the implication that recent studies with more robust study designs (i.e., prospective studies vs. currently utilized ecological studies) be sought for utilization in the assessment. Recent studies document lower exposures in populations more similar to the U.S. population in genetic background, diet and lifestyle. In the five years that have ensued since our review of the 2005 draft document, epidemiology studies (with a more robust prospective study design and individual exposure assessment) have examined cancer outcomes at reasonably well documented arsenic drinking water levels ≤ 100 μg/L. While the February 2010 USEPA draft document did review a large number, but not all, of these studies and presented tabled results (Appendix B) as suggested by SAB (2007), the draft did not present a review of each study conducted by systematic consistent application of the uniform performance criteria called out in the 2007 SAB Arsenic Review Panel report (SAB, 2007, p.39).[8]

Indeed, a review of the epidemiological literature is important because these newer studies provide additional evidence supporting a threshold effect. As Exponent stated, "The epidemiological data at low doses in Southwest Taiwan and in other studies consistently reflect a sublinear dose-response relationship or threshold for significant risk below an arsenic concentration in water around 100 to 200 ug/l."[9] Specifically, both the

[8] Id.
[9] March 29 Exponent Comment at 2.

2010 draft and the Work Group Report fail to even acknowledge the recent Mink meta-analysis that provides the most recent and strongest evidence of a threshold effect. We agree with Gradient that there was no "meaningful synthesis of the data or any effort to reconcile disparate or similar data."[10] Thus, it is critical that EPA perform this analysis, just as it needs to correct its work relative to the mode of action studies.

Again, the Work Group failed to significantly address these studies, or the conclusion supporting the existence of a drinking water threshold. The best the Work Group could offer was that EPA needed to "more clearly state the criteria", and "should consider summarizing major studies since 2007."[11]

C. Dose –Response Modeling and Robustness of Estimates

The EPA draft review claims that EPA's draft cancer slope estimate is robust, even when evaluated under other reasonable modeling scenarios.[12] However, as several commenters noted, EPA's estimates only appear robust because the Agency arbitrarily, and inconsistently with the 2007 SAB advice, failed to examine the situation where there is a nonlinear dose response curve (the most likely scenario, as judged by knowledgeable scientists), combined with the absence of the comparison population.

As related by Gradient in its March 29th comments:

> The draft states (p. F-6), "when no reference population is included, and when inappropriate statistical models are employed, it is possible to find insignificant or negative dose-response relationships for InAs for some portions of the date. When appropriate models are used, however, the Taiwanese data show robust and significant positive associations…even in low-exposure groups." This statement evinces a tactic of dismissing the concerns of the earlier SAB review and its call for exploration of these issues through narrow technical considerations, attempting to address the letter of SAB's recommendations while making sure to avoid the substance and spirit. It is not evident that the analyses without an external reference population are not "appropriate"; indeed, the questions about the comparability of the external populations used to the study area and the evident great impact that their inclusion has on the fitted curves, especially in view of the way that inclusion of an external point ruins the fit of the curve to the low-dose villages that are actually within the study area, argues that such analyses are very much a part of the proper characterization of the Taiwan study results.[13]

EPA states that its estimate is only not robust if one employs an "inappropriate model," without explaining why the nonlinear model and no reference population was somehow

[10] March 29 Gradient Comment at 5.
[11] May 13 Work Group Draft Report at 4-5.
[12] 2010 EPA Toxicological Review at 142-143.
[13] March 29 Gradient Comments at ll.

inappropriate. The Work Group report simply parrots the EPA discussion that the estimates are robust, saying that "none of the alternative models materially changed the estimated risk levels versus use of a linear model."[14]

EPA further indicates that it found no evidence of the low-dose threshold in its own modeling, and the Work Group concurs with that observation. However, more recent literature and the commenters have demonstrated how the Taiwan data is most consistent with a low-dose drinking water threshold.

In addition, the commenters were very specific about several modeling problems with the EPA approach. They described the use of an inappropriate comparison population (see below), the misclassification of low dose villages with high exposure wells, and the assumption that the comparison population had no arsenic in their drinking water. Both the Work Group review and the EPA draft generally ignored these issues.

D. Use of Comparison Population

EPA has not requested advice from the SAB on the use of the reference population since 2001, and therefore, another key critical element of the Review remains unexamined in both 2007 and 2010. The derived cancer potency slope is highly dependent on EPA's use of the Southwest Taiwan area as a comparison population to the study area population. As others have noted, there is substantial doubt that this reference population is comparable to the study group, which is required for the use of a valid reference population.

At the April 6/7 meeting, EPA appeared to be unaware of the evidence that the reference population had much higher cancer rates than the study population, for reasons unrelated to arsenic. These differences were the subject of both verbal and written comments to the Work Group.

However, the best the Work Group report offers is to ask EPA to include the rationale for using the comparison population from the 2005 issue paper (that had never been subject to peer review) in the report, and describe the reference population in more detail. To its credit, the Work Group did admit that exclusion of the reference population "did have an effect on risk estimates" – but didn't ask EPA to explain this further.[15]

[14] May 13 Work Group Draft Report at 6.
[15] Id.

IV. Conclusion

In sum, the serious procedural issues and the rushed schedule made it almost impossible for the Work Group to perform a serious and independent review. The 2010 draft failed in many respects to address key scientific issues. The above discussion makes it clear EPA has much additional work to do to complete the 2010 Draft.

The commenter listed as "B. Smarte, PhD, Former EPA Fellow and Concerned Citizen" asks: "When will EPA take comment on and conduct a scientific review of the scientific choices and judgments that have been made since 2005?" He points out that several of the EPA 2010 "choices, inputs, judgments and decision points" may not even have been addressed in the 2007 SAB recommendations.

> "The regulatory implications of a new IRIS value are too great to skip the step which should have included scientific review of EPA's final determination, informed by the 2007 SAB recommendations. The public has been waiting many years for this revision. It is of critical importance not to skip one of the most crucial steps: public comment and external ***scientific (***bold italics in original***)*** review."[16]

The SAB was established in 1978 to "provide independent advice and peer review" on EPA science. It can decline to challenge EPA science and just become another reviewing office at EPA, or it can ensure that the 2010 review gets a proper independent peer review, based on its Congressional charter and the most current science.

We understand that the results of significant new research may be forthcoming in the next year or so, and that may be a better time to restart this review. For the sake of the SAB and scientific integrity, we hope that the SAB will make the right choice and terminate this review.

[16] EPA-HQ-ORD-2010-0123-0020 at p. 2.